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(12) Patent:

(11) CA 929483

(54) PROCESS FOR PREPARING SUBSTITUTED PHENYLALKANOIC ACIDS

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ABSTRACT:

CLAIMS: [Show all claims](#)

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Last Modified: 2002-12-31[Important Notices](#)

PROCESS FOR PREPARING SUBSTITUTED PHENYLALKANOIC ACIDS**Patent number:** CA929483**Also published as:****Publication date:** 1973-07-03 ES413738 (A)**Inventor:** SLETZINGER M [US]; LY M [US]; PINES S [US];
KARADY S [US]**Applicant:** MERCK & CO INC**Classification:****- International:****- european:****Application number:** CA19700078420 19700325**Priority number(s):** CA19700078420 19700325

Abstract not available for CA929483

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1 This invention relates to a process for preparing
2 L- α -hydrazino- β -phenylpropionic acids.

3 More particularly, this invention relates to a
4 process for preparing L- α -hydrazino- β -phenylpropionic acids
5 by photolytically decomposing an azidoformamido acid.

6 It is known in the art that various α -hydrazino- β -
7 phenylpropionic acids are useful as decarboxylase inhibitors.
8 It is further known that the D-isomer of these acids is
9 generally inactive and may even be antagonistic to the
10 action of the L-form, thereby reducing its potency.

11 In the past, it has been the accepted practice to
12 separate stereoisomers by the formation of diastereomeric
13 salts with either optically active bases or acids, depending
14 on the nature of the racemate. However, with the hydrazino
15 compounds of the present invention, separation is complicated
16 by the fact that some diastereomeric salts do not form crys-
17 talline materials with sufficiently different properties so
18 that the diastereomers can be readily crystallized. In some
19 instances, the diastereomeric salts are oily or waxy materials
20 which become difficult if not impossible to separate by con-
21 ventional means. Quite obviously, if a relatively simple and
22 inexpensive process could be found which would preferentially
23 produce the desired L- α -hydrazino- β -phenylpropionic acids, it
24 would receive widespread acceptance in the art.

25 Accordingly, it is an object of this invention to
26 provide a process for preparing L- α -hydrazino- β -phenylpro-
27 pionic acids. Other objects will become apparent from the
28 ensuing description of this invention.



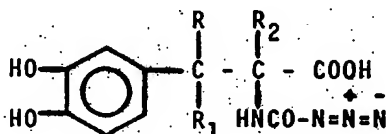
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These objects are accomplished by the present invention which provides a process for preparing the L-form of a compound of the formula:



wherein:

R, R₁ and R₂ each may be hydrogen or loweralkyl;
which comprises photolytically decomposing the L-form of a compound of the formula:



wherein:

R, R₁ and R₂ are as previously defined.

10

As used above the "loweralkyl" radical signifies an alkyl group containing from 1 to about 6 carbon atoms which can be straight chained or branched.

In order to obtain the starting materials for the above photolysis reaction the corresponding L-α-amino-β-phenyl-propionic acid is reacted with phosgene and sodium azide.

The photolysis reaction of this invention preferably takes place in the presence of water and may be carried out at a temperature of from about -50°C. to about +100°C., preferably -20°C. to +20°C.

20

The following examples are presented to further illustrate the invention.

EXAMPLE 1

2 L- α -hydrazino- α -methyl- β -(3,4-dihydroxyphenyl)propionic acid
3 L- α -methyl-3,4-dihydroxyphenylalanine sesquihydrate
4 (119.1 g., 0.5 mole) and toluene are placed in a flask and
5 refluxed. By means of a Dean-Stark* separator water is azeo-
6 troped away and toluene is returned to the flask. When the
7 theoretical amount of water is distilled the mixture is con-
8 centrated to dryness in vacuo. The residue is taken up in
9 500 ml. of methanol and the mixture saturated at 0-5°C. with
10 gaseous hydrogen chloride. The mixture is allowed to stand
11 at 0°C. for 42 hours and is then concentrated to dryness to
12 yield L- α -methyl-3,4-dihydroxyphenylalanine methyl ester.

To the ester (67.58 g., 0.3 mole) from the previous step slurried with tetrahydrofuran (1 l.) at 55-70°C. is passed phosgene at the rate of 0.5 mole per hour. After two hours nitrogen is bubbled through the mixture as it is allowed to cool to room temperature. The solution is concentrated in vacuo to obtain L- α -chlorocarbonyl- α -methyl- β -(3,4-carboxyldioxyphenyl)alanine methyl ester.

The ester of the previous step is taken up in dimethoxyethane (500 ml.), powdered sodium azide (19.5 g., 0.3 mole) is added and with stirring the mixture is refluxed for 3 hours. The mixture is filtered, the filtrate concentrated in vacuo to dryness and the residue crystallized from acetone-hexane to yield L- α -N-azidocarbonyl- α -methyl- β -(3,4-carboxyldioxyphenyl)alanine methyl ester.

27 The ester (32.03 g., 0.1 mole) so obtained is
28 stirred overnight at 25°C. with 1 N hydrochloric acid (100
29 ml.). The mixture is concentrated in vacuo to dryness to
30 yield L- α -N-azidocarbonyl- α -methyl- β -(3,4-dihydroxyphenyl)

* t. m.

alanine. To the residue is added 300 ml. of water and the mixture warmed to 80°C. with stirring then cooled to 0°C. The mixture is photolysed at 0°C. with a low pressure mercury arc. The mixture is diluted to 1 l. with water, warmed to 90°C., filtered and the filtrate cooled to room temperature. The cooled filtrate was absorbed on Amberlite-IR-120[®] on the acid (H₃O⁺) cycle. Elution with 1 N ammonium hydroxide and concentration of the eluate to dryness in vacuo yields crude product. On recrystallization L-α-hydrazino-α-methyl-β-(3,4-dihydroxyphenyl)propionic acid is obtained.

EXAMPLE 2

L-α-hydrazino-β-(3,4-dihydroxyphenyl)propionic acid

L-3,4-dihydroxyphenylalanine (98.6 g., 0.5 mole) is taken up in 500 ml. of methanol and the mixture saturated at 0-5°C. with gaseous hydrogen chloride. The mixture is allowed to stand at 0°C. for 42 hours and is then concentrated to dryness to yield L-3,4-dihydroxyphenylalanine methyl ester.

To the ester (63.37 g., 0.3 mole) from the previous step slurried with tetrahydrofuran (1 l.) at 55-70°C. is passed phosgene at the rate of 0.5 mole per hour. After two hours nitrogen is bubbled through the mixture as it is allowed to cool to room temperature. The solution is concentrated in vacuo to obtain L-α-chlorocarbonyl-β-(3,4-carboxyldioxyphenyl)alanine methyl ester.

The ester of the previous step is taken up in dimethoxyethane (500 ml.), powdered sodium azide (19.5 g., 0.3 mole) is added and with stirring the mixture is refluxed for 3 hours. The mixture is filtered, the filtrate concentrated in vacuo to dryness and the residue crystallized from acetone-hexane to yield L-α-N-azidocarbonyl-β-(3,4-carboxyldioxyphenyl)alanine methyl ester.

1 The ester (30.62 g., 0.1 mole) so obtained is
 2 stirred overnight at 25°C. with 1 N hydrochloric acid (100
 3 ml.). The mixture is concentrated in vacuo to dryness to
 4 yield L- α -N-azidocarbonyl- β -(3,4-dihydroxyphenyl)alanine.
 5 To the residue is added 300 ml. of water and the mixture
 6 warmed to 80°C. with stirring then cooled to 0°C. The mix-
 7 ture is photolysed at 0°C. with a low pressure mercury arc.
 8 The mixture is diluted to 1 l. with water, warmed to 90°C.,
 9 filtered and the filtrate cooled to room temperature. The
 10 cooled filtrate was absorbed on Amberlite-IR-120[®] on the acid
 11 (H_3O^+) cycle. Elution with 1 N ammonium hydroxide and con-
 12 centration of the eluate to dryness in vacuo yields crude
 13 product. On recrystallization L- α -hydrazino- β -(3,4-dihydroxy-
 14 phenyl)propionic acid is obtained.

15 EXAMPLE 3

16 L- α -ethyl- α -hydrazino- β -(3,4-dihydroxyphenyl)propionic acid
 17 L- α -ethyl-3,4-dihydroxyphenylalanine (112.6 g.,
 18 0.5 mole) is taken up in 500 ml. of methanol and the mixture
 19 saturated at 0-5°C. with gaseous hydrogen chloride. The
 20 mixture is allowed to stand at 0°C. for 42 hours and is then
 21 concentrated to dryness to yield L- α -ethyl-3,4-dihydroxy-
 22 phenylalanine methyl ester.

23 To the ester (71.8 g., 0.3 mole) from the pre-
 24 vious step slurried with tetrahydrofuran (1 l.) at 55-70°C.
 25 is passed phosgene at the rate of 0.5 mole per hour. After
 26 two hours nitrogen is bubbled through the mixture as it is
 27 allowed to cool to room temperature. The solution is con-
 28 centrated in vacuo to obtain L- α -chlorocarbonyl- α -ethyl- β -
 29 (3,4-carbonyldioxyphenyl)alanine methyl ester.

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1 The ester of the previous step is taken up in
2 dimethoxyethane (500 ml.), powdered sodium azide (19.5 g.,
3 0.3 mole) is added and with stirring the mixture is refluxed
4 for 3 hours. The mixture is filtered, the filtrate concen-
5 trated in vacuo to dryness and the residue crystallized
6 from acetone-hexane to yield L- α -N-azidocarbonyl- α -ethyl- β -
7 (3,4-carbonyldioxyphenyl)alanine methyl ester.

8 The ester (33.43 g., 0.1 mole) so obtained is
9 stirred overnight at 25°C. with 1 N hydrochloric acid (100
10 ml.). The mixture is concentrated in vacuo to dryness to
11 yield L- α -N-azidocarbonyl- α -ethyl- β -(3,4-dihydroxyphenyl)-
12 alanine. To the residue is added 300 ml. of water and the
13 mixture warmed to 80°C. with stirring then cooled to 0°C.
14 The mixture is photolysed at 0°C. with a low pressure mercury
15 arc. The mixture is diluted to 1 l. with water, warmed to
16 90°C., filtered and the filtrate cooled to room temperature.
17 The cooled filtrate was absorbed on Amberlite-IR-120[®] on
18 the acid (H₃O⁺) cycle. Elution with 1 N ammonium hydroxide
19 and concentration of the eluate to dryness in vacuo yields
20 crude product. On recrystallization L- α -ethyl- α -hydrazino-
21 β -(3,4-dihydroxyphenyl)propionic acid is obtained.

22 EXAMPLE 4

23 L- α -hydrazino- α , β -dimethyl- β -(3,4-dihydroxyphenyl)propionic
24 acid

25 L- α , β -dimethyl-3,4-dihydroxyphenylalanine (112.6 g.,
26 0.5 mole) is taken up in 500 ml. of methanol and the mixture
27 saturated at 0-5°C. with gaseous hydrogen chloride. The mix-
28 ture is allowed to stand at 0°C. for 42 hours and is then
29 concentrated to dryness to yield L- α , β -dimethyl-3,4-dihydroxy-
30 phenylalanine methyl ester.

1 To the ester (71.8 g., 0.3 mole) from the previous
2 step slurried with tetrahydrofuran (1 l.) at 55-70°C. is
3 passed phosgene at the rate of 0.5 mole per hour. After two
4 hours nitrogen is bubbled through the mixture as it is
5 allowed to cool to room temperature. The solution is con-
6 centrated in vacuo to obtain L- α -chlorocarbonyl- α,β -dimethyl-
7 β -(3,4-carbonyldioxyphenyl)alanine methyl ester.

8 The ester of the previous step is taken up in
9 dimethoxyethane (500 ml.), powdered sodium azide (19.5 g.,
10 0.3 mole) is added and with stirring the mixture is refluxed
11 for 3 hours. The mixture is filtered, the filtrate concen-
12 trated in vacuo to dryness and the residue crystallized
13 from acetone-hexane to yield L- α -N-azidocarbonyl- α,β -dimethyl-
14 β -(3,4-carbonyldioxyphenyl)alanine methyl ester.

15 The ester (33.43 g., 0.1 mole) so obtained is
16 stirred overnight at 25°C. with 1 N hydrochloric acid (100
17 ml.). The mixture is concentrated in vacuo to dryness to
18 yield L- α -N-azidocarbonyl- α,β -dimethyl- β -(3,4-dihydroxyphenyl)-
19 alanine. To the residue is added 300 ml. of water and the
20 mixture warmed to 80°C. with stirring then cooled to 0°C.
21 The mixture is photolysed at 0°C. with a low pressure mer-
22 cury arc. The mixture is diluted to 1 l. with water, warmed
23 to 90°C., filtered and the filtrate cooled to room tempera-
24 ture. The cooled filtrate was absorbed on Amberlite-IR-120[®]
25 on the acid (H₃O⁺) cycle. Elution with 1 N ammonium hydroxide
26 and concentration of the eluate to dryness in vacuo yields
27 crude product. On recrystallization L- α -hydrazino- α,β -
28 dimethyl- β -(3,4-dihydroxyphenyl)propionic acid is obtained.

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EXAMPLE 5

L- α -hydrazino- α,β,β -trimethyl- β -(3,4-dihydroxyphenyl) propionic acid

L- α,β,β -trimethyl-3,4-dihydroxyphenylalanine (119.6 g., 0.5 mole) is taken up in 500 ml. of methanol and the mixture saturated at 0-5°C. with gaseous hydrogen chloride. The mixture is allowed to stand at 0°C. for 42 hours and is then concentrated to dryness to yield L- α,β,β -trimethyl-3,4-dihydroxyphenylalanine methyl ester.

To the ester (75.99 g., 0.3 mole) from the previous step slurried with tetrahydrofuran (1 l.) at 55-70°C. is passed phosgene at the rate of 0.5 mole per hour. After two hours nitrogen is bubbled through the mixture as it is allowed to cool to room temperature. The solution is concentrated in vacuo to obtain L- α -chlorocarbonyl- α,β,β -trimethyl-(3,4-carbonyldioxyphenyl)alanine methyl ester.

The ester of the previous step is taken up in dimethoxyethane (500 ml.), powdered sodium azide (19.5 g., 0.3 mole) is added and with stirring the mixture is refluxed for 3 hours. The mixture is filtered, the filtrate concentrated in vacuo to dryness and the residue crystallized from acetone-hexane to yield L- α -N-azidocarbonyl- α,β,β -trimethyl- β -(3,4-carbonyldioxyphenyl)alanine methyl ester.

The ester (34.83 g., 0.1 mole) so obtained is stirred overnight at 25°C. with 1 N hydrochloric acid (100 ml.). The mixture is concentrated in vacuo to dryness to yield L- α -N-azidocarbonyl- α,β,β -trimethyl- β -(3,4-dihydroxyphenyl)alanine. To the residue is added 300 ml. of water and the mixture warmed to 80°C. with stirring then cooled to 0°C. The mixture is photolysed at 0°C. with a low pressure

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1 mercury arc. The mixture is diluted to 1 l. with water,
2 warmed to 90°C., filtered and the filtrate cooled to room
3 temperature. The cooled filtrate was absorbed on Amberlite-
4 IR-120^B on the acid (H₃O⁺) cycle. Elution with 1 N ammonium
5 hydroxide and concentration of the eluate to dryness in vacuo
6 yields crude product. On recrystallization L- α -hydrazino-
7 α,β,β -trimethyl- β -(3,4-dihydroxyphenyl)propionic acid is
8 obtained.

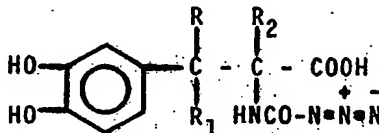
The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A process for preparing the L-form of a compound of the formula:



wherein:

R, R₁ and R₂ each may be hydrogen or loweralkyl;
which comprises photolytically decomposing the L-form of a compound of the formula:



wherein:

R, R₁ and R₂ are as previously defined.

2. The process of Claim 1 wherein the photolysis reaction is carried out in the presence of water.

3. The process of Claim 2 wherein the photolysis reaction is carried out at a temperature of from about -20°C. to about +20°C.

4. The process of Claim 1 wherein R and R₁ are hydrogen and R₂ is methyl.

5. The process of Claim 1 wherein R, R₁ and R₂ are all hydrogen.



ABSTRACT OF THE DISCLOSURE

Process for converting L- α -amino- β -phenyl propionic acids to L- α -hydrazino- β -phenylpropionic acids by photolytically decomposing an azidocarbonyl group in the presence of water at a temperature range of from -50°C . to about $+100^{\circ}\text{C}$.

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